The Eating Disorders
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Chapter 7

Gastrointestinal Peptides and the Limitation of Meal Size

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Research into the physiological mechanisms controlling food intake has a long and varied history. Two major theories have dominated this research until recently. One proposed a role for glucose metabolism in meal initiation (the "glucostatic hypothesis") [1], and the other proposed roles for hypothalamic hunger and satiety "centers" in body weight regulation [2,3]. In spite of decades of experimental work, however, so many inconsistencies, conflicts, and gaps persist in each of these theories that new tactics have evolved.

One of the fastest growing of these new tactics is the attempt to determine whether gastrointestinal peptides are decisive in ending a meal. The logic here is that, since a wide variety of peptides are rapidly released into blood by ingested food as it stimulates the stomach and small intestine, some of these peptides might act as negative feedback signals to stop eating—in other words, they might function as "satiety signals."

Even before synthetic or highly purified peptides became available, several studies suggested that crude or partially purified gut extracts might decrease food intake [4-7]. In 1972, three gut hormones had become available in relatively pure form: gastrin, from gastric mucosa; secretin; and cholescystokinin (CCK), from duodenal mucosa. We began to test each of these peptide hormones to determine if they would decrease food intake.

CHOLECYSTOKININ AS A PARADIGM FOR A SATIETY SIGNAL

Secretin and gastrin failed to decrease food intake, but the initial results using CCK were striking. Intraperitoneal injections of a 10% pure preparation of CCK caused a large and clearly dose-related inhibition of solid food intake [8] (figure 1).

It was apparent that the rats in these early tests with CCK were not incapacitated in any obvious way. Further inspection revealed that CCK was not preventing or delaying the approach to food when it was offered at the beginning of each test. Instead, it was shortening the duration of the test meal—a characteristic consistent with a satiety action [9].

In a series of follow-up studies, we then put CCK through several tests of behavioral specificity. It reduced liquid food intake even more effectively than it reduced solid food intake, demonstrating that the reduction did not represent an impairment of specific motor movements involved in grasping and chewing solid food. CCK did not change core body temperature. CCK failed to reduce water intake when rats were water deprived; it did, however, produce the characteristic potent dose-related reduction of liquid food intake when the same rats were food deprived. This behavioral dissociation argues powerfully against the possibility that some subclinical malaise or slight discomfort is the mechanism of action of CCK [8].

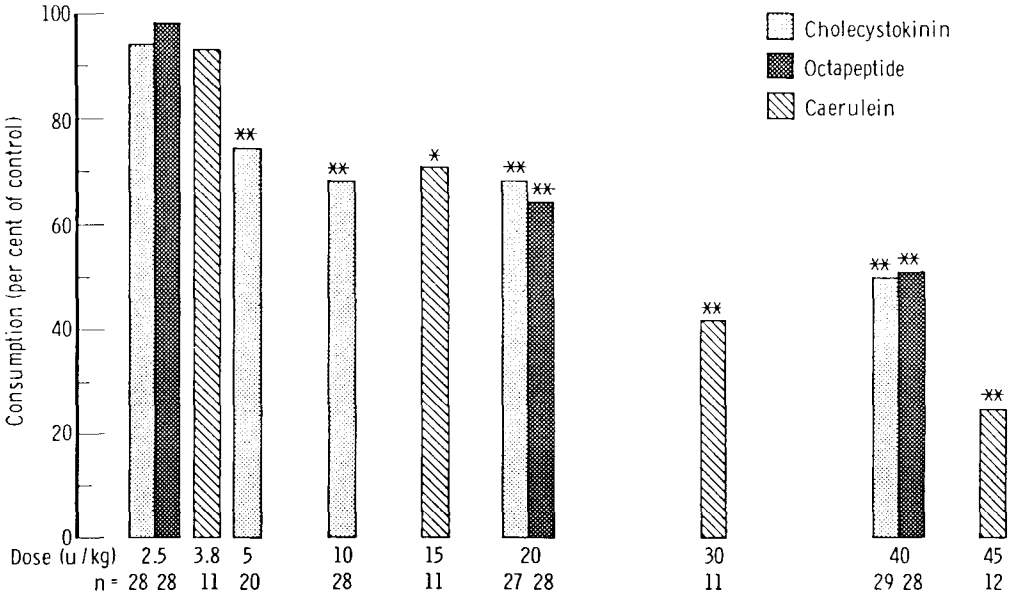

Figure 7.1 Consumption of solid food (expressed as a percent of control consumption) during the first 30 minutes following intraperitoneal injection of impure cholecystokinin (lighter bars), the synthetic C-terminal octapeptide of cholecystokinin (darker bars), or caerulein (hatched bars). Each substance produced a dose-related suppression of food intake. One unit of impure cholecystokinin is equivalent to approximately 0.05 μg of the synthetic octapeptide in biological activity. Doses of caerulein were calculated by assuming that it was 15 times as potent by weight as impure cholecystokinin (A. Anastasi, personal communication). Mean control intakes ranged from 2.8-4.3g. Statistical differences from control intakes after vehicle injection of 0.15 M NaCl: *$p < 0.01$; $p < 0.001$.

Because only an impure extract containing CCK had been employed in the initial tests, we next sought evidence for chemical specificity. Systemic injections of the biologically active synthetic C-terminal octapeptide of CCK (CCK-8) and the related decapeptide ceruletide produced inhibitory effects on food intake that were similar to those produced by the original impure preparation (figure 1). Desulfated CCK-8, a biologically weak analogue, did not inhibit food intake [10]. Large doses of gastrin, chemically similar to CCK, were also ineffective.

In an attempt to determine the potency of CCK, we next prepared rats with chronic indwelling gastric cannulas that could be temporarily opened at a test meal to allow the rapid drainage of all of an ingested liquid food. When rats were first tested with the gastric cannulas open, the results were surprising—feeding was virtually continuous for hours [11]. Thus, under these test conditions, when little or no food accumulated in the stomach or stimulated the small intestine, satiety was absent. This fact made a test of CCK's presumed satiety action even more interesting, because CCK originates in the small intestine. The results of the test were clear, and can be seen in figure 2. CCK inhibited sham feeding, demonstrating its potency in a situation in which there was no gastric distention and food stimulation of the small intestine was absent or minimal [10].

Additional persuasive evidence that the inhibition of sham feeding by CCK represented a state of satiety appeared in this test. CCK not only inhibited sham feeding, but it elicited the fixed sequence of behaviors that normally characterize the end of a meal in rats: grooming, locomotion and rearing, and finally resting [12].

The results of tests with CCK in rats were encouraging enough to lead to investigations in other species. CCK, administered systemically, has been examined for a satiety-like action in mice [13-15], chickens [16], rabbits [17], sheep [18], pigs [19], and rhesus monkeys [20]. The success of this last study led to tests in humans. Under double-blind conditions, slow intravenous infusions of CCK produced reductions of meal size ranging from 15% to 50% in lean men and women [21,22] and in obese men [23]. These infusions, all in the low-nanogram-dose range, failed to produce any evidence of toxicity or significant side effects. Thus, the results of objective tests in rats, indicating that CCK was producing satiety, not malaise, predicted the subjective experience of humans, who reported that they felt normal satiety, not malaise [24].

The peripheral and central routes that exogenous CCK uses when it produces the behavioral and subjective state of satiety are incompletely known. It is known

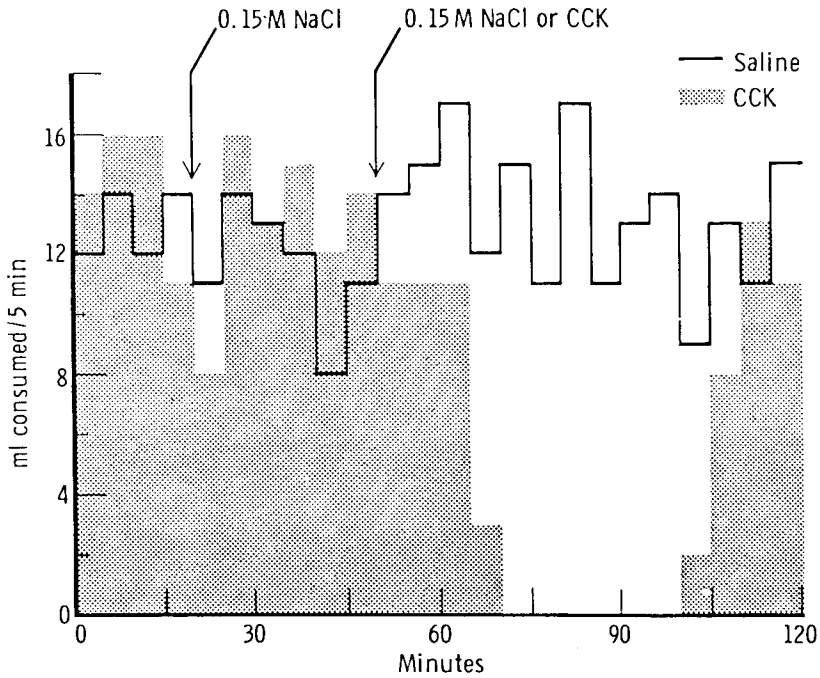

Figure 7.2 Sham consumption of diluted liquid food (in ml) by one representative rat on a day when impure cholecystokinin was injected intraperitoneally in a dose of 40 units- kg^{-1} (shaded area) and on an adjacent day when equivolumetric vehicle (0.15 m NaCl) was injected (line). Cholecystokinin produced a rapid, complete, and transient inhibition of food intake.

that the full action of peripherally-administered CCK-8 is crucially dependent on the subdiaphragmatic vagus [25,26] and that the important elements of this vagal requirement are gastric [25] and afferent [27]. Based on studies in rhesus monkeys, McHugh has suggested that the satiety effect of exogenous CCK is indirect and dependent on the peptide's inhibition of gastric emptying and a resultant gastric distention [28]. Such an indirect action of circulating CCK on the stomach might then be mediated by gastric vagal afferents to the brain stem.

An outline of important brain areas mediating the satiety action of systemically-injected CCK in the rat may now be emerging. Within the brain stem, electrolytic lesions of the area postrema-nuclear tractus solitarius (the latter a target for vagal afferents) may attenuate the effect of intraperitoneally administered CCK [29]. Within the diencephalon, lesions of the paraventricular nucleus (a target for nucleus tractus solitarius afferents) [29] (JN Crawley, personal communication) or the dorsomedial nucleus [30] also attenuate the effect of intraperitoneally administered CCK. Finally, observations of injections of low concentrations of CCK-8 into the fourth ventricle [31], overlying the nucleus tractus solitarius, into the third ventricle (E Stellar, personal communication) or directly into the paraventricular nucleus [32] suggest that these injections may mimic actions of neuronal CCK, perhaps in nucleus tractus solitarius and paraventricular nucleus. At this point, however, these observations remain only suggestions. Baile and his colleagues, based on extensive work since 1979, have produced strong support for their conclusion that central CCK is primarily responsible for satiety in sheep [33].

There is another major area of ignorance in the CCK puzzle. Does the satiety action of exogenous CCK have physiological meaning? No one has produced the critical evidence needed to decide whether endogenous CCK exerts a limiting effect on meal size under normal conditions in animals or humans. It is known that apparently low doses of exogenous CCK-8 (50ng-kg^1 in rats) [34] (30ng- kg^{-1} in humans) [21] inhibit food intake. But this is not critical evidence, because reliable radioimmunoassays that agree on the absolute levels of the multiple circulating forms of CCK in human or rat plasma are required to allow comparisons with levels achieved after such doses of exogenous CCK. These radioimmunoassays are not available at present. Furthermore, the straightforward measurement of circulating CCK levels may provide incomplete information. It seems extremely unlikely the CCK could be the only satiety signal, and much more likely that it would interact with other satiety signals released by the action of food on the surface of the gut. In fact, Moran

and McHugh have demonstrated striking potentiation of the satiating effect of a low dose (4ng- kg^{-1}-min^{-1}) of CCK-8 by gastric distention in the rhesus monkey [35]. Thus, it will be hazardous to categorize satiety candidates as pharmacological or physiological until the important candidates are identified and their interactions are quantified.

OTHER PUTATIVE SATIETY PEPTIDES

Bombesin (BBS) is one of several peptides isolated from amphibian skin by Erspamer and his colleagues during the 1970s (for review, see reference 36). This research effort has proved to be of great importance, because families of peptides closely resembling the amphibian ones have been identified throughout the mammalian gut and brain [37,38]. We found that intraperitoneal injections of BBS produced effects on food intake in rats that were remarkably similar to those of CCK. BBS caused rapid, large, dose-related inhibitions that were behaviorally specific and without obvious side effects [39,40]. Gastrin-releasing peptide (GRP), a mammalian counterpart of amphibian BBS, had similar effects in rats [41], in mice [42], and in baboons [43]. In the one test to date in humans, an intravenous infusion of BBS (4 ng/kg^{-1}-min^{-1}) decreased meal size without producing significant side effects [44].

Because the satiety characteristics of BBS were so remarkably similar to those of CCK, we tested the effect of subdiaphragmatic vagotomy on BBS-induced satiety. In contrast to its blockade of CCK-induced satiety, vagotomy did not alter the satiety potency of BBS [45]. This dissociation demonstrated that the mechanisms of action of the two peptides are different; BBS does not produce satiety in rats solely by releasing endogenous CCK. Collins and his colleagues [46], using the CCK antagonist proglumide, have obtained independent results supporting this conclusion. In addition, Bellinger and Bernardis showed that dorsomedial hypothalamic lesions significantly attentuated the suppression of feeding by CCK, but not by BBS [30].

Although we now know that the mechanism of action of BBS on food intake is different from that of CCK, we do not know what the mechanism is. Furthermore, no endocrine or neural ablation has been shown to block its action. Presently, we are combining vagal and spinal disconnections in an attempt to block the satiety effect of peripherally-injected BBS.

In the late 1950s, shortly after pure pancreatic glucagon became available, it was administered to human volunteers in attempts to reduce the subjective sense of hunger [47] and to produce weight loss [48]. Both attempts were successful. These early results in humans have been followed up by animal studies showing that the inhibition by glucagon was specific for food intake and did not reduce water intake, and that, like CCK and BBS, glucagon exerted its satiety-like action during the last portion of the meal, without altering the initial rate of feeding [49].

Martin and Novin, in the earliest search for a mechanism of action for glucagon, found that hepatic-portal infusions of this peptide produced a dose-related inhibition of food intake [50]. VanderWeele and his colleagues showed that subdiaphragmatic vagotomy blocked glucagon-induced satiety [51,52]. Geary and Smith found that selective hepatic vagotomy blocked the effect, whereas selective gastric or selective coeliac vagotomy did not [53]; Bellinger and Williams, however, failed to modify the inhibitory action of glucagon on feeding by a presumed complete liver denervation [54].

As is well known, the major effect of glucagon at the liver is glycogenolysis. Although this seemed the obvious choice for a hepatic mechanism of action, Geary and Smith [55] demonstrated clear evidence against this possibility: They showed that glucagon produced a marked hepatic vein hyperglycemia (via hepatic glycogenolysis) when it was injected just before sham feeding, but that it failed to have any effect on sham feeding. Thus, hepatic vein hyperglycemia is not sufficient as a mechanism of action for glucagon-induced satiety.

Strong evidence that the satiety action of exogenous glucagon reflects a physiological action of the endogenous hormone came from the study of Langhans et al [56], when they demonstrated that the acute administration of antiglucagon antibodies to rats produced a large increase in meal size. If this result can be replicated, and the specificity of the antibody can be shown under the behavioral test conditions, the results will constitute the strongest evidence yet supporting a physiological role for any putative satiety signal.

Other peptides that have been shown to reduce food intake under some circumstance in at least one species include somatostatin [57,58], calcitonin [59,60], pancreatic polypeptide [61,62,42], and thyrotropin-releasing hormone [63-66]. The available evidence supporting a true satiety role for any of these peptides fails to meet the standards applied above to CCK, BBS, and pancreatic glucagon.

CONCLUSION

Three peripheral peptides—cholecystokinin, bombesin, and pancreatic glucagon—produce potent inhibitions of food intake and exert constellations of behavioral effects in several species, which make each one a se-

rious candidate for a physiological role in regulating meal size. Cholecystokinin is by far the most thoroughly investigated candidate. Nevertheless, in no case has a physiological role for any of the three peptides been demonstrated, and in no case is the mechanism of action understood. In the setting of this volume, a final caution deserves emphasis: How the limiting effect of these peptides on experimental meal size might relate to the deranged controls of feeding behavior and body weight seen in patients with eating disorders remains intriguing, but almost entirely unknown.

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